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Continued use of afatinib with the addition of cetuximab after progression on afatinib in patients with *EGFR* mutation-positive non-small-cell lung cancer and acquired resistance to gefitinib or erlotinib☆

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ABSTRACT

Objectives: In a phase Ib trial, afatinib plus cetuximab demonstrated promising clinical activity (objective response rate [ORR]: 29%; median progression-free survival [PFS]: 4.7 months) in patients with *epidermal growth factor receptor* (*EGFR*) mutation-positive non-small-cell lung cancer (NSCLC) with acquired resistance to erlotinib or gefitinib. Here, a separate cohort exploring afatinib plus cetuximab after progression on afatinib is reported.
Materials and methods: Patients with *EGFR* mutation-positive NSCLC who progressed on erlotinib or gefitinib received afatinib 40 mg daily until progression, followed by afatinib daily plus cetuximab 500 mg/m^2 every 2 weeks until progression or intolerable adverse events (AEs). Endpoints included safety, ORR, and PFS.
Results: Thirty-seven patients received afatinib monotherapy. Two (5%) patients responded; median PFS was 2.7 months. Thirty-six patients transitioned to afatinib plus cetuximab. Four (11%) patients responded; median PFS was 2.9 months. Median PFS with afatinib plus cetuximab for patients who received afatinib monotherapy for $\geq$12 versus < 12 weeks was 4.9 versus 1.8 months (p = 0.0354), and for patients with T790M-positive versus T790M-negative tumors was 4.8 versus 1.8 months (p = 0.1306). Fifty percent of patients receiving afatinib plus cetuximab experienced drug-related grade 3/4 AEs. The most frequent drug-related AEs (any grade) were diarrhea (70%), rash (49%), and fatigue (35%) with afatinib monotherapy and rash (69%), paronychia (39%), and dry skin (36%) with afatinib plus cetuximab.
Conclusion: Sequential EGFR blockade with afatinib followed by afatinib plus cetuximab had a predictable safety profile and demonstrated modest activity in patients with *EGFR* mutation-positive NSCLC with resistance to erlotinib or gefitinib.
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1. Introduction

Epidermal growth factor receptor (*EGFR*) mutation-positive (*EGFR*m+) non-small-cell lung cancer (NSCLC) tumors are extremely sensitive to the EGFR tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib, and afatinib, all of which are approved as first-line treatment in this setting [1–8]. Unfortunately, tumors inevitably develop resistance to these agents. The most common resistance mechanism is the emergence of the T790M *EGFR* mutation within exon 20, occurring in approximately 50% of patients [9–11]. While osimertinib, a third-generation EGFR TKI, has recently been approved for patients with T790M-positive (T790M+) NSCLC with progression following EGFR TKI therapy, treatment options for EGFR TKI-resistant NSCLC remain limited, especially in patients with T790M-negative (T790M−) tumors [12].

In contrast to erlotinib and gefitinib, which inhibit only EGFR, afatinib is an ErbB family blocker that irreversibly blocks signaling from all relevant homo- and hetero-dimers of the ErbB family of receptors (EGFR, human epidermal growth factor receptor 2 [HER2], ErbB3, and ErbB4) [13]. The recent phase IIb trial, LUX-Lung 7, demonstrated that afatinib conferred better progression-free survival (PFS) and time to treatment failure versus gefitinib in patients with previously untreated NSCLC, suggesting that the broader inhibitory profile of afatinib may offer advantages in terms of clinical activity in a first-line setting [14]. Also, given that ErbB family members have been implicated in the acquired resistance to first-generation EGFR TKIs [15,16], and afatinib has shown inhibitory activity against *EGFR* T790M/L858R tumors in preclinical models (albeit at relatively high concentrations) [17], there was rationale for assessing afatinib monotherapy in patients with *EGFR* mutation-positive NSCLC following failure of erlotinib or gefitinib. However, in clinical trials, afatinib conferred only modest response rates in this setting [18,19]. Nevertheless, afatinib-based combinations warrant clinical evaluation, due to potential synergy with other agents. One potential strategy is dual targeting of EGFR [20].

Cetuximab, an anti-EGFR monoclonal antibody, is approved for the treatment of KRAS wild-type colorectal and head and neck cancers. In mice harboring tumors with L858R/T790M mutations, afatinib plus cetuximab resulted in extensive tumor regression greater than what was observed with either agent alone [20]. We therefore conducted a study to determine the maximum tolerated dose (MTD), safety, and preliminary efficacy of afatinib plus cetuximab in patients with *EGFR*-mutant tumors and acquired resistance to erlotinib/gefitinib. We previously reported that afatinib plus cetuximab in these patients was associated with an objective response rate (ORR) of 29% [21]. Based on these data, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC, version 3, 2017, state that afatinib plus cetuximab may be considered in patients with disease progression on EGFR TKI therapy (category 2A evidence and consensus) [22]. Here, we report pharmacokinetic data from the afatinib plus cetuximab cohort, and efficacy and safety data from an additional cohort that was treated with afatinib monotherapy followed, upon progression, by afatinib plus cetuximab (at the MTD previously established). Given that afatinib-based combinations have previously demonstrated activity in patients with acquired resistance to afatinib monotherapy following ≥12 weeks of clinical benefit [19], and development of T790M is the predominant mechanism of acquired resistance to afatinib [11], we also assessed the efficacy of afatinib plus cetuximab according to the duration of prior afatinib monotherapy (< 12 weeks; ≥12 weeks) and T790M status.

2. Materials and methods

2.1. Study design

This open-label, phase Ib study was conducted in three phases: a dose-finding phase to identify the MTD of afatinib plus cetuximab, an expansion phase to evaluate the MTD (previously reported) [21], and a sequential phase assessing afatinib monotherapy until disease progression and afatinib plus cetuximab thereafter (Fig. 1). The primary endpoint was occurrence of dose-limiting toxicities. Secondary endpoints included safety, pharmacokinetics, PFS, ORR, and disease control rate (DCR).

Upon observation of efficacy in patients treated at MTD (afatinib 40 mg p.o. daily plus cetuximab 500 mg/m^2 i.v. every 2 weeks), the sequential phase was added to assess the safety and antitumor activity of afatinib with cetuximab in patients with *EGFR*-mutant NSCLC with acquired resistance to erlotinib or gefitinib, who had progressed on afatinib monotherapy. Those patients who progressed after at least 12 weeks of disease control on afatinib monotherapy were defined as having acquired resistance to afatinib.

The study was conducted in compliance with the International Conference on Harmonization and Good Clinical Practice guidelines and the protocol was approved by the relevant institutional review boards. Patients provided written informed consent prior to study participation.

2.2. Patients

Patients with confirmed stage IIIb/IV NSCLC harboring *EGFR* mutations associated with EGFR TKI sensitivity or exon 20 insertions or de novo *T790M* mutation were eligible. Participants had progressed on continuous erlotinib/gefitinib within 30 days of initiation of study treatment [23]. Patients had to stop erlotinib/gefitinib for ≥3 days prior to starting afatinib [24]. Additional inclusion criteria were adequate organ function and Eastern Cooperative Oncology Group performance status of 0–2. Exclusion criteria included prior treatment with EGFR-targeting antibodies, symptomatic brain metastases, interstitial lung disease, radiotherapy within 2 weeks, and systemic chemotherapy, hormonal therapy, immunotherapy, or experimental or approved antibody/proteins within 30 days of starting study treatment.

2.3. Treatment

Patients received afatinib 40 mg p.o. daily until disease progression and then continued afatinib with added cetuximab 500 mg/m^2 i.v. given every 2 weeks (patients who had dose reduction during afatinib monotherapy maintained their afatinib dose). Patients who had received afatinib monotherapy in other trials, and progressed after ≥12 weeks, could be enrolled into the combination therapy phase of this study. Patients received combination therapy within 30 days of progression on monotherapy with no intervening systemic therapy.

Treatment continued until disease progression, intolerable adverse events (AEs), study withdrawal, or death. Treatment beyond progression was allowed at the investigator's discretion. Management of AEs by dose reduction was prespecified. For the MTD (afatinib 40 mg/cetuximab 500 mg/m^2), on first occurrence of grade ≥3 AEs (other than hypomagnesemia where only cetuximab was to be reduced), cetuximab was reduced by 100 mg to 400 mg, and on second occurrence, afatinib and cetuximab were reduced (by 10 mg to 30 mg for afatinib and by 100 mg to 300 mg for cetuximab). Dose reduction below afatinib 30 mg was not permitted. A maximum of one cetuximab infusion per cycle could be skipped to allow recovery from drug-related AEs.

2.4. Assessments

EGFR mutation analysis was mandatory prior to study entry and was undertaken on fresh or archived tumor tissues, in a Clinical Laboratory Improvement Amendments-certified laboratory. Re-biopsy following disease progression while on study was optional. Mutations in exons 18–21 of the tyrosine kinase domain of EGFR were analyzed by polymerase chain reaction-restriction fragment length polymorphism-based assays or direct Sanger sequencing.

Nomenclature

Abbreviations

AE	Adverse event
AR	Acquired resistance
$AUC_{\tau,ss}$	Area under the concentration–time curve of the analyte in plasma at steady state over a uniform dosing interval τ
CI	Confidence interval
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval
CR	Complete response
DCR	Disease control rate
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
gCV	Geometric coefficient of variation
gMean	Geometric mean
HER2	Human epidermal growth factor receptor 2
i.v.	Intravenous
MTD	Maximum tolerated dose
NCCN	National comprehensive cancer network
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
p.o.	Per os (oral administration)
PR	Partial response
Q2W	Every 2 weeks
SD	Stable disease
TKI	Tyrosine kinase inhibitor

AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [25]. Tumor assessments, performed by computed tomography at baseline, weeks 4, 8, and 12, and every 8 weeks thereafter, were assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 [26].

2.5. Pharmacokinetic analysis

Pharmacokinetic analysis focused on afatinib plus cetuximab, and analyzed patients in the dose-escalation phase and the first 24 patients enrolled in the MTD expansion phase. Blood samples were taken at predefined intervals from the start of the study to the third treatment course (see Supplementary Material A1, for the blood sample collection schedule). Plasma concentrations of afatinib were analyzed by a validated high performance liquid chromatography–tandem mass spectrometry assay with a minimum detection level of 1.25 ng/mL; serum concentrations of cetuximab were analyzed by a validated enzyme-linked immunosorbent assay with a minimum detection level of 12500 ng/mL.

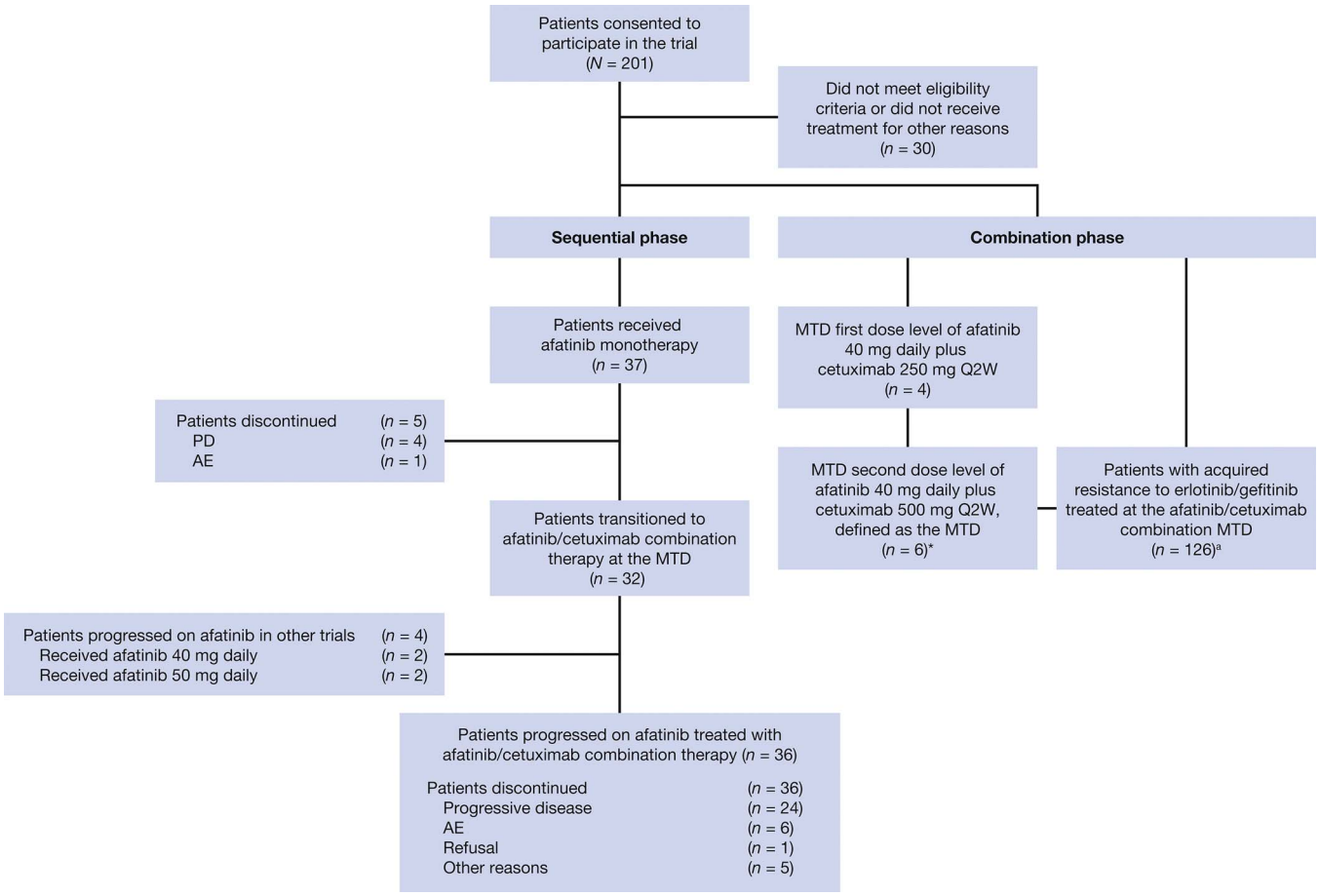

Fig. 1. Study design and patient disposition. Abbreviations: AE, adverse event; MTD, maximum tolerated dose; PD, progressive disease; Q2W, every 2 weeks. *Previously reported Janjigian Y, et al. [21] [a]Including the six patients treated in the dose-finding phase previously reported by Janjigian Y, et al. [21].

2.6. Statistical analysis

Safety and antitumor activity were assessed in patients with acquired resistance to erlotinib/gefitinib who received ≥1 dose of afatinib, and in patients who received ≥1 dose of afatinib and cetuximab. Descriptive statistics were used. Exploratory analyses of the sequential phase summarized antitumor activity and PFS according to the duration of previous afatinib monotherapy (≥12 weeks or < 12 weeks) and T790M mutation status. PFS was analyzed using Kaplan–Meier methodology.

3. Results

3.1. Patient population

A total of 201 patients were enrolled and 171 were treated across the three study phases. Of these, 10 were treated in the dose-finding phase (including six treated at MTD of afatinib 40 mg daily plus cetuximab 500 mg/m^2 every 2 weeks) and 120 were treated at MTD in the expansion phase (previously reported) [21]. For the sequential phase, 37 patients received afatinib monotherapy; 32 entered the combination phase. Four patients were enrolled into the combination phase from other afatinib monotherapy trials (and had previously progressed on erlotinib/gefitinib; Fig. 1).

Patients in the sequential phase had received prior EGFR TKI treatment for a median of 1 year (range, < 1–6; Table 1). Approximately 70% of patients had Del19-positive (Del19+) tumors; one patient had an exon 20 insertion. T790M status was known for all patients in the sequential phase: approximately 55% were T790M+ and 45% were T790M− (Table 1).

3.2. Efficacy

Median time on treatment was 2.8 months (range, 0.2–14.7) with afatinib monotherapy. Two of 37 patients (5%) achieved a confirmed objective response by week 4 and 12, respectively (confirmed partial responses [PRs]; Table 2). Median duration of response was 3.9 months (range, 3.8–3.9). One of the two patients who responded had a T790M + tumor. DCR on afatinib monotherapy was 57%.

Thirty-two patients from the monotherapy phase and four patients from other afatinib trials were treated in the combination phase. Median time on treatment was 2.6 months (range, 0.5–21.6). Four patients (11.1%) achieved a confirmed objective response (all PRs; Table 2), three of whom had acquired resistance to afatinib monotherapy. Two PRs were achieved by week 4, the third by week 8, and the fourth after week 32. Median duration of response was 5.7 months (range, 3.7–8.3). None of the patients who responded during the combination phase had responded to afatinib monotherapy. The ORR was numerically higher in patients who received ≥12 weeks versus < 12 weeks of prior afatinib monotherapy (15.8% and 5.9%; Table 2) and in patients who had T790M+ versus T790M− tumors (20.0% and 0.0%; Table 2). Overall, the DCR in patients who received combination therapy was 50.0%. The DCR according to duration of prior afatinib monotherapy was 57.9% (≥12 weeks) and 41.2% (< 12 weeks). The DCR according to T790M status was 60.0% (T790M+) and 37.5% (T790M−), respectively. Outcomes following combination therapy were similar in patients whose tumors were Del19+ (n = 25; DCR = 48.0%; ORR = 12.0%) and L858R+ (n = 9; DCR = 44.4%; ORR = 11.1%).

Median PFS was 2.7 months (95% confidence interval [CI]: 1.1–3.7) and 2.9 months (95% CI: 1.8–4.8) in the monotherapy and combination phases, respectively (Table 2, Fig. 2). PFS on combination therapy was significantly longer in patients who received ≥12 weeks versus < 12 weeks of afatinib monotherapy (4.9 months and 1.8 months; p = 0.0354; Table 2). PFS in patients who had T790M+ versus T790M− tumors was 4.8 months and 1.8 months, respectively (p = 0.1306; Table 2). Median PFS among patients with Del19+ tumors was 2.7 and 2.9 months with afatinib monotherapy and afatinib plus cetuximab, respectively. For those with L858R+ tumors, median PFS was 3.6 and 1.8 months with afatinib monotherapy and afatinib plus cetuximab, respectively. One patient with an exon 20 insertion who received afatinib plus cetuximab had stable disease at weeks 4 and 8; the patient died from an unrelated stroke on day 107. PFS status for individual patients is shown in Fig. 3.

Given the signals of clinical activity in patients who had T790M+ tumors, or had received ≥12 weeks of afatinib monotherapy, we undertook further exploratory analysis assessing outcomes in patients with T790M+ tumors and/or ≥12 weeks of afatinib monotherapy (see Supplementary Table S1, for response and PFS according to acquired resistance and T790M status). Despite small patient numbers, PFS and ORR were numerically higher in the T790M+/ ≥ 12 weeks and T790M +/ < 12 weeks groups compared with the T790M−/ < 12 weeks

Table 1
Patient characteristics at baseline.

Characteristic	Sequential phase	
	Afatinib 40 mg monotherapy (n = 37)	Afatinib 40 mg Cetuximab 500 mg/m^2 (n = 36)
Age, years		
Median (range)	58 (34–80)	58 (27–80)
Female gender, no. (%)	23 (62.2)	22 (61.1)
Race, no. (%)		
Asian	5 (13.5)	5 (13.9)
Black/African American	1 (2.7)	1 (2.8)
White	31 (83.8)	30 (83.3)
Smoking history, no. (%)		
Never smoked	25 (67.6)	25 (69.4)
≤15 pack years	7 (18.9)	7 (19.4)
> 15 pack years	2 (5.4)	2 (5.6)
Missing	3 (8.1)	2 (5.6)
ECOG PS, no. (%)		
0	9 (24.3)	8 (22.2)
1 or 2	28 (75.7)	28 (77.8)
Time since diagnosis of NSCLC,[a] years		
Median (range)	2 (1–15)	2 (1–15)
Duration of prior EGFR TKI,[b] years		
Median (range)	1 (< 1–6)	1 (< 1–6)
Prior chemotherapy, no. (%)		
0 or 1 line	25 (67.6)	24 (66.7)
≥2 lines	12 (32.4)	12 (33.3)
EGFR mutation status, no. (%)		
Del19+	26 (70.3)	25 (69.4)
L858R+	9 (24.3)	9 (25.0)
Other	2 (5.4)[c]	2 (5.6)[d]
T790M status, no. (%)		
T790M+	20 (54.1)	20 (55.6)
T790M–	17 (45.9)	16 (44.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

[a] Available for 34 patients in the monotherapy phase and 33 patients in the combination therapy phase of the sequential phase, respectively.

[b] Maximum duration if patients received more than one prior EGFR TKI regimen.

[c] One patient had a de novo T790M mutation (and did not participate in the combination phase), the other patient had *G719C* and *L861Q* mutations.

[d] One patient (who was enrolled from another trial following progression on afatinib monotherapy) had an exon 20 insertion, the other patient had *G719C* and *L861Q* mutations.

Table 2
Efficacy in the dose-escalation phase and in the monotherapy and combination therapy phases of the sequential phase.

		Afatinib/cetuximab combination therapy (n = 36)						
	Afatinib monotherapy (n = 37)	Total	≥12 weeks Afatinib monotherapy (n = 19)	< 12 weeks Afatinib monotherapy (n = 17)	p Value	T790M+ (n = 20)	T790M− (n = 16)	p Value
DCR, no. (%)	21 (56.8)	18 (50.0)	11 (57.9)	7 (41.2)	0.3189	12 (60.0)	6 (37.5)	0.0512*
ORR, no. (%)	2 (5.4)	4 (11.1)	3 (15.8)	1 (5.9)	0.3630	4 (20.0)	0 (0)	0.0823**
CR	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
PR	2 (5.4)	4 (11.1)	3 (15.8)	1 (5.9)		4 (20.0)	0 (0)	
SD	19 (51.4)	14 (38.9)	8 (42.1)	6 (35.3)		8 (40.0)	6 (37.5)	
PD	13 (35.1)	11 (30.6)	4 (21.1)	7 (42.1)		3 (15.0)	8 (50.0)	
NE	3 (8.1)	3 (17.6)	4 (21.1)	3 (17.6)		5 (25.2)	2 (12.5)	
Median duration of disease control, months (range)	4.2 (0.0–14.7)	4.8 (0.0–19.3)	5.9 (1.8–19.3)	4.5 (0.0–6.5)		4.8 (0.0–19.3)	3.6 (1.8–11.1)	
Median duration of objective response, months (range)	3.9 (3.8–3.9)	5.7 (3.7–8.3)	7.4 (3.9–8.3)	3.7 (3.7–3.7)		5.7 (3.7–8.3)	–	
Median PFS, months (95% CI)	2.7 (1.1–3.7)	2.9 (1.8–4.8)	4.9 (1.6–10.1)	1.8 (0.9–4.5)	0.0354	4.8 (1.8–5.9)	1.8 (0.9–4.5)	0.1306***

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

* Logistic regression p value.

** Fishers exact test p value.

*** Log-rank test p value.

group. Furthermore, in the T790M−/ ≥ 12 weeks group, median PFS was 10.1 months and the DCR was 50%. Notably, two patients in this group demonstrated encouraging PFS of 10.1 and 11.1 months, respectively (Fig. 3), indicating that absence of T790M+ does not preclude prolonged PFS as long as afatinib confers benefit for ≥12 weeks.

3.3. Safety

Ninety-seven percent of patients receiving afatinib monotherapy reported drug-related AEs; 35% experienced grade 3 events and no drug-related grade 4/5 AEs were reported. The most frequent drug-related AEs (any grade) included diarrhea (70%), rash (49%), fatigue (35%), and stomatitis (27%) (Table 3).

In the combination phase, 94% of patients reported drug-related AEs, with 50% experiencing grade 3/4 AEs (16 [44%] reported grade 3 AEs; 2 [6%] reported grade 4 AEs). There were no drug-related grade 5 AEs. The most frequent drug-related AEs (any grade) were rash (69%), paronychia (39%), dry skin (36%), and diarrhea (33%).

Drug-related serious AEs were reported in two patients receiving afatinib monotherapy (grade 3 decreased appetite and diarrhea; grade < 3 dehydration, nausea, and vomiting) and one patient receiving afatinib plus cetuximab (grade 3 chills and pyrexia).

Five patients (14%) receiving afatinib monotherapy required dose reduction for AEs; three patients (8%) reported grade 3 events, including diarrhea (5%) and rash (3%). These patients entered into the combination phase at a reduced starting dose of afatinib 30 mg/day plus cetuximab 500 mg/m^2. Eight patients (22%) receiving afatinib and cetuximab required dose reduction due to AEs, primarily due to rash (14%). Treatment discontinuation due to drug-related AEs was necessary in three patients (8%) receiving afatinib plus cetuximab (cough, rash [grade 4], and skin infection [grade 3]). There were no treatment discontinuations during the afatinib monotherapy phase.

3.4. Pharmacokinetics

Afatinib exposure was higher in the afatinib 40 mg plus cetuximab 250 mg/m^2 group versus the afatinib 40 mg plus cetuximab 500 mg/m^2 group. However, considering the large difference in patient numbers and variability between groups, afatinib pharmacokinetic parameters were considered similar in the presence of different cetuximab doses (see Supplementary Fig. S1 and Supplementary Table S2, for pharmacokinetic parameters of afatinib alone and with cetuximab). Observed cetuximab serum concentrations were compared with historical data using a population pharmacokinetic model-based approach. There was no evidence that afatinib had a clinically relevant effect on exposure to cetuximab (see Supplementary Material A2 and Supplementary Table S3, for observed and simulated cetuximab serum concentrations).

4. Discussion

Sequential use of afatinib monotherapy followed by afatinib plus cetuximab was feasible in patients with *EGFR* mutation-positive NSCLC with acquired resistance to erlotinib or gefitinib. In particular, patients with T790M+ tumors and/or those who received ≥12 weeks of afatinib monotherapy demonstrated signals of clinical activity to this regimen. Overall, treatment discontinuations due to treatment-related AEs were low. Pharmacokinetic data suggested no relevant drug–drug interactions between afatinib and cetuximab.

Afatinib monotherapy was associated with an ORR of 5%, DCR of 57%, and median PFS of 2.7 months in patients with acquired resistance to erlotinib/gefitinib. These results are consistent with those in the phase IIb/III LUX-Lung 1 trial, which enrolled patients with advanced NSCLC who had received prior chemotherapy and progressed on erlotinib or gefitinib. The ORR on afatinib was 7%; median PFS was 3.3 months [18]. Following progression on monotherapy, afatinib plus cetuximab led to an ORR of 11%, DCR of 50%, and median PFS of 2.9 months. In the previously reported upfront combination phase of our study, afatinib plus cetuximab resulted in an ORR of 29%, DCR of 89%, and median PFS of 4.7 months [21]. However, it is not possible to compare the relative efficacy of afatinib plus cetuximab in the sequential and combination cohorts of the study, given differences in the patient populations.

Overall incidence of drug-related AEs was similar when afatinib and cetuximab were used as an upfront combination (99% all grades and 46% grade 3/4) [21] or after afatinib (94% all grades and 50% grade 3/4), as were discontinuations due to drug-related AEs (13% with upfront combination [21] and 8% after afatinib). However, incidence of drug-related diarrhea and rash was lower with the sequential regimen (33% and 69% all grades) than the combination regimen (71% and 90% all grades) [21]. This may have been partly because patients in the

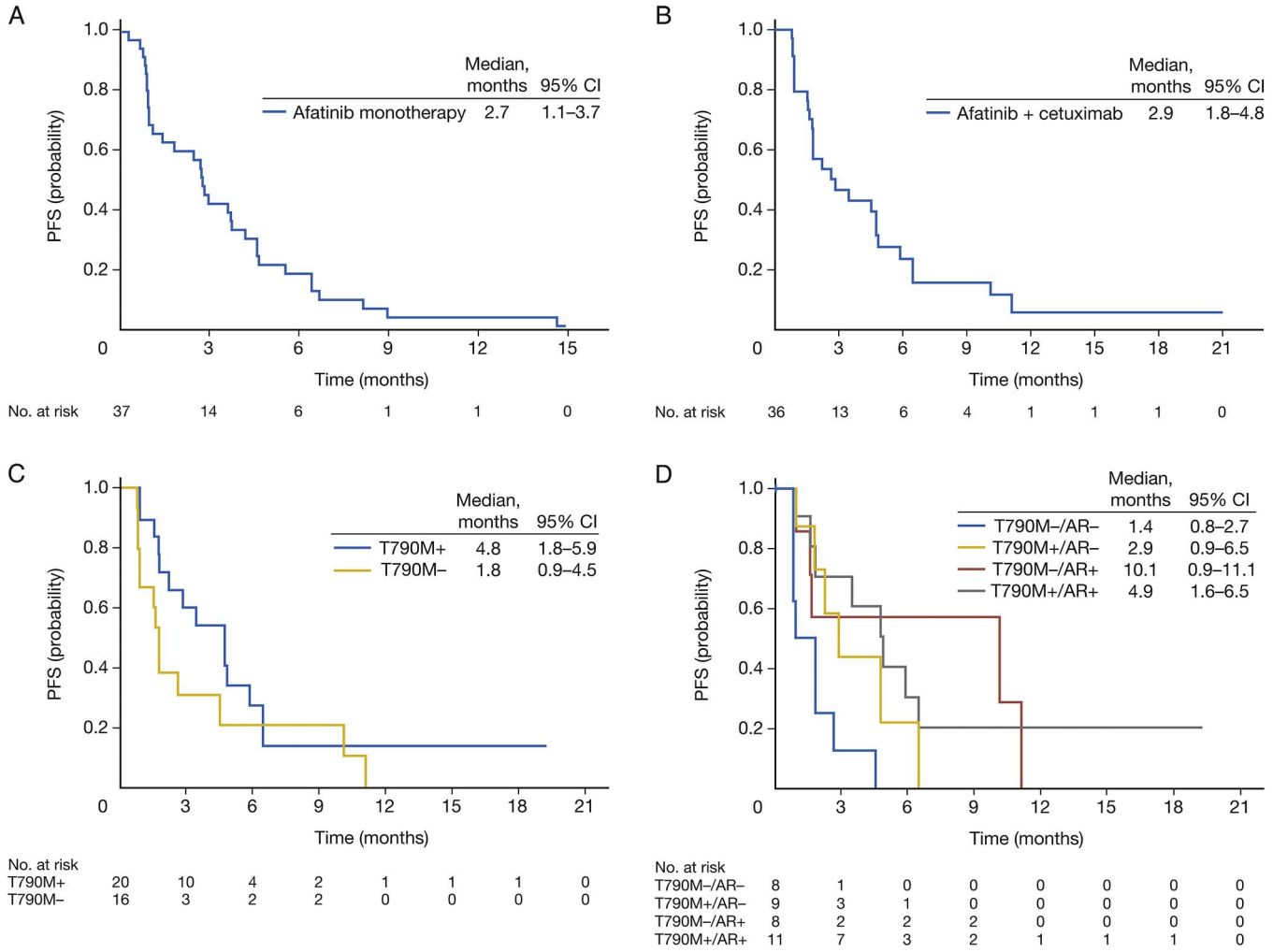

Fig. 2. Kaplan–Meier curves of PFS in (A) the monotherapy phase of the sequential phase; (B) the combination phase of the sequential phase; (C) the combination phase of the sequential phase according to T790M status; (D) the combination portion of the sequential phase according to T790M status and duration of prior afatinib monotherapy (< 12 weeks; ≥12 weeks). CI, confidence interval; PFS, progression-free survival.
Note: symbols on the lines indicate censored patients.

sequential phase were able to dose reduce to afatinib 30 mg monotherapy and remain on that dose when they received the combination. Furthermore, in the sequential regimen, patients received afatinib monotherapy first, which was associated with a lower incidence of drug-related grade 3/4 events than afatinib plus cetuximab (35% vs 50%, respectively). Therefore, sequential treatment may offer an alternative approach for patients for whom achieving a response may not be as important or where tolerability, particularly rash or diarrhea, may be a concern. Additionally, for those who have already progressed on afatinib monotherapy, the addition of cetuximab may offer further clinical benefit. An ongoing phase II/III trial will provide further information on the safety of afatinib monotherapy versus afatinib plus cetuximab in EGFR TKI-naive patients with *EGFR* mutation-positive advanced NSCLC (NCT02438722).

Although numbers are small, exploratory analysis suggests that patients with T790M+ tumors respond better to afatinib plus cetuximab than those with T790M tumors following afatinib monotherapy. Since this trial was conceived and commenced, third-generation EGFR TKIs such as osimertinib and olmutinib (in South Korea only) have been approved for the treatment of patients with confirmed T790M mutations and have conferred remarkable activity as second-line therapy in this setting (ORRs of ~60%) [27,28]. Given these observations, the regimen described herein is unlikely to constitute a major treatment option immediately following acquired resistance to a first-line EGFR TKI in most cases. It may, however, have a role in patients who have progressed following a third-generation TKI, or cannot tolerate these agents. Furthermore, observations in this study suggest that presence of T790M is not a prerequisite for sensitivity to combination therapy; DCR and PFS were also promising in patients who received ≥12 weeks of treatment with afatinib monotherapy, regardless of T790M status, with two patients demonstrating PFS of nearly a year. Furthermore, in the previous analysis of upfront afatinib plus cetuximab, response rates were very similar in T790M+ (32%) and T790M− (25%) tumors [21]. Therefore, the combination warrants further evaluation in the T790M− setting, an area of significant unmet medical need.

The mechanism for the efficacy of afatinib plus cetuximab has not been elucidated but may be because they bind to different parts of the receptor (intracellular and extracellular, respectively) [29]. Afatinib also induces redistribution of EGFR to the cell surface [30]. The broad ErbB inhibition of afatinib may be important as HER2 amplification has been implicated in resistance to EGFR TKIs and cetuximab [31]. Interestingly, erlotinib plus cetuximab failed to produce any objective responses in patients with acquired resistance to erlotinib or gefitinib [32].

In conclusion, sequential blockade of ErbB family receptors with afatinib followed by afatinib plus cetuximab had a predictable safety profile and showed activity in heavily pretreated patients with acquired resistance to erlotinib or gefitinib. Further clinical evaluation of afatinib plus cetuximab is warranted.

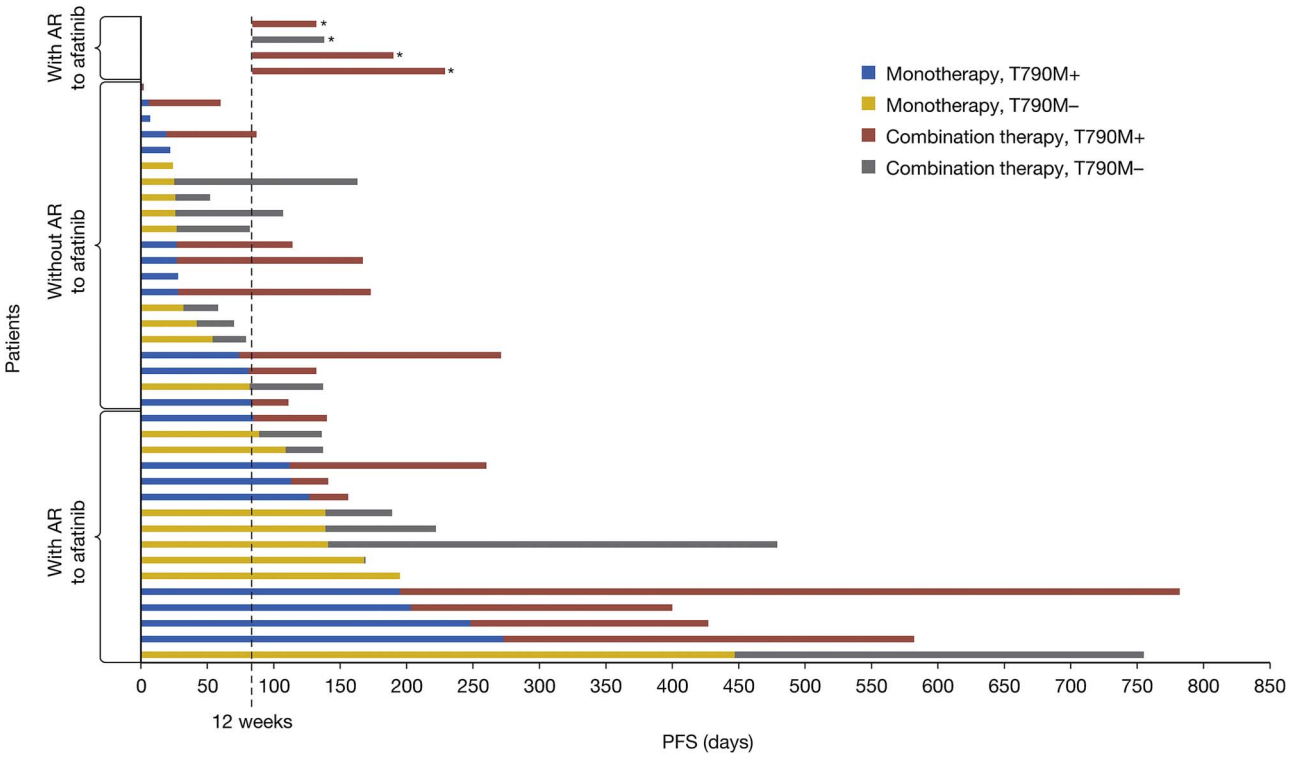

Fig. 3. Duration of PFS for individual patients on afatinib monotherapy followed by afatinib and cetuximab combination therapy. AR, acquired resistance; PFS, progression-free survival. *Received afatinib monotherapy in other trials and had ≥12 weeks of benefit.

Table 3
Treatment-related AEs occurring in ≥10% of patients in either the monotherapy or combination phases of the sequential arm.

	Afatinib 40 mg monotherapy (n = 37)			Afatinib/cetuximab combination therapy (n = 36)		
AE, no. (%)	Total	Grade 3[a]	Grade 4	Total	Grade 3[b]	Grade 4
Total with related AEs	36 (97.3)	13 (35.1)	0	34 (94.4)	16 (44.4)	2 (5.6)
Diarrhea	26 (70.3)	2 (5.4)	0	12 (33.3)	0	0
Rash + +	18 (48.6)	1 (2.7)	0	25 (69.4)	7 (19.4)	1 (2.8)
Fatigue +	13 (35.1)	3 (8.1)	0	10 (27.8)	0	0
Stomatitis +	10 (27.0)	0	0	4 (11.1)	0	0
Headache	8 (21.6)	2 (5.4)	0	8 (22.2)	2 (5.6)	0
Acne/dermatitis acneiform + +	7 (18.9)	0	0	9 (25.0)	2 (5.6)	0
Nausea	7 (18.9)	0	0	7 (19.4)	0	0
Paronychia +	7 (18.9)	0	0	14 (38.9)	0	0
Vomiting	6 (16.2)	0	0	2 (5.6)	0	0
Dizziness	5 (13.5)	0	0	2 (5.6)	0	0
Dry skin	5 (13.5)	0	0	13 (36.1)	0	0
Pyrexia	5 (13.5)	0	0	5 (13.9)	1 (2.8)	0
Cough	4 (10.8)	0	0	3 (8.3)	0	0
Decreased appetite	4 (10.8)	1 (2.7)	0	2 (5.6)	0	0
Dyspnea	4 (10.8)	1 (2.7)	0	1 (2.8)	1 (2.8)	0
Epistaxis	4 (10.8)	0	0	2 (5.6)	0	0
Rhinorrhea	3 (8.1)	0	0	4 (11.1)	0	0
Hypomagnesemia	2 (5.4)	0	0	10 (27.8)	0	1 (2.8)
Alopecia	2 (5.4)	0	0	5 (13.9)	0	0
Chills	2 (5.4)	0	0	4 (11.1)	1 (2.8)	0
Pruritus	1 (2.7)	0	0	6 (16.7)	0	0
Dry mouth	0	0	0	4 (11.1)	0	0

Abbreviations: AE, adverse event.
Note: + and + + indicate grouped terms.
[a] Additional grade 3 treatment-related events with afatinib monotherapy comprised: back pain, n = 1; hypokalemia, n = 1; hyponatremia, n = 1; upper respiratory tract infection, n = 1; and syncope, n = 1.
[b] Additional grade 3 treatment-related events with afatinib and cetuximab combination therapy comprised: blood magnesium decreased, n = 1; hypophosphatemia, n = 2; eyelid infection, n = 1; hypokalemia, n = 1; hyponatremia, n = 1; neutrophilic dermatosis, n = 1; presyncope, n = 1; and skin infection, n = 1.

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The sponsor was involved in the trial design and managed the clinical trial database. Data were collected by the investigators and were analyzed jointly with the sponsor. All authors, including those employed by the sponsor, were responsible for data interpretation and the development of the article, and approved the final version for submission.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.lungcan.2017.08.014.

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